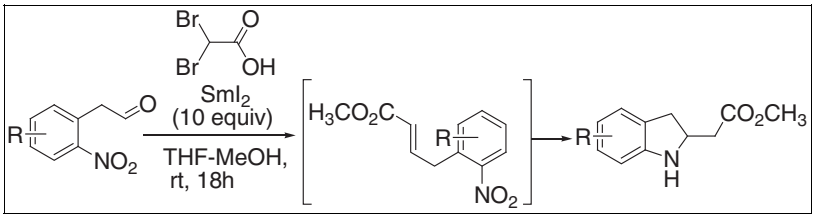
Synthesis of Indolines via a SmI_2 Promoted Domino Nitro Reduction–Intramolecular *aza*-Michael Reaction

Josierika A. Ferreira Ramos,[a] Carolina S. Araújo,[a] Tanus J. Nagem,[a] and Jason G. Taylor[a]*

Departamento de Química (DEQUI), ICEB, Universidade Federal de Ouro Preto, Campus Morro do Cruzeiro, CEP. 35400-000, Ouro Preto, Minas Gerais, Brazil
*E-mail: jason@iceb.ufop.br

Received January 19, 2013
DOI 10.1002/jhet.1982
Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com).



A simple and straightforward synthesis of substituted indolines based on a domino nitro reduction intramolecular *aza*-Michael reaction is described. The reaction employs Samarium diiodide under mild conditions for the addition of dibromoacetic acid to substituted 2-(2-nitrophenyl) acetaldehyde derivatives and their subsequent cyclization upon nitro group reduction to provide corresponding indoline heterocycles in good yields. This "one pot" strategy also permitted the expeditious synthesis of a 1,2,3,4-tetrahydroquinoline, whereas the seven-membered 2,3,4,5-tetrahydrobenzoazepines compounds were not formed under these reaction conditions.

J. Heterocyclic Chem., **00,** 00 (2014).

INTRODUCTION

Compounds with biological activity that have found applications as pharmaceuticals and agricultural chemicals are often derived from nitrogen heterocyclic structures, which also appear frequently in natural products [1,2]. Nitrogen heterocycles pertinent to this work include indoline and 1,2,3,4-tetrahydroquinoline structures, and a variety of synthetic methodologies for the synthesis of these structures have been summarized in many reviews [3,4]. Examples of the indoline structural framework can be encountered in natural products such as JBIR-16 [5] and (2*S*)-cyclo-Dopa-5-*O*-glucoside [6] (Fig. 1).

Despite the wide availability of synthetic methods, there still exists a need to develop more efficient procedures, particularly those that allow the synthesis of indoline intermediates with pendant functional groups, which could later be exploited for the preparation of other complex azapolycyclic ring systems. The intramolecular *aza*-Michael reaction offers a direct and atom-economical means of efficiently synthesizing nitrogen heterocycles. It is known that in the presence of triphenylphosphine, that azide functional group bearing acyclic -α,β-unsaturated carbonyl and cyano compounds spontaneously cyclize upon reduction to afford pyrrolidines or piperidines in good yields [7]. Furthermore, carbamates and sulfonamides can undergo intermolecular cyclizations with α,β-unsaturated carbonyl compounds in the presence of a simple base such as sodium *tert*-butoxide or sodium hydrogen carbonate [8–12] (Scheme 1). An article relevant to this work was published in the year 2000 in which Bunce and coworkers demonstrated that the exploitation of a nitro group in a tandem reduction–intramolecular Michael addition protocol could efficiently provide nitrogen heterocycles such as 2-(tetrahydroquinolin-2-yl)-, 2-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)- and 2-(tetrahydroquinoxalin-2-yl) acetates in good yield when simply employing iron powder in glacial acetic (Scheme 1) [13]. In a similar fashion, the formation of five-membered rings as part of a tricyclic molecule via a tandem reduction–Michael addition from a nitro group has been developed for the synthesis of hexahydrocarbazoles [14]. However, on this occasion, the α,β-unsaturated carbonyl compound is a cyclic enone, and the acyclic version was never explored.

Thus, proof of concept had been established for the synthesis of aryl fused six-membered ring nitrogen heterocycles and our curiosity lead us to investigate the possibility of analogous five- and seven-membered compounds being conveniently accessed in a similar manner. Facile synthesis of the requisite precursor for the domino reaction would render this approach synthetically useful for its application in a longer multistep synthesis. In this regard, herein, we report the application of a domino nitro reduction–intramolecular *aza*-Michael strategy that occurs in a one pot fashion upon coupling of dibromoacetic acid with of substituted 2-(2-nitrophenyl) acetaldehyde derivatives in the presence of SmI_2 to afford substituted indoline derivatives.

RESULTS AND DISCUSSION

The synthesis of the target precursor begins with a simple nucleophilic substitution reaction of commercially available substituted 2-nitrotoluenes **1a–f** with paraformaldehyde in

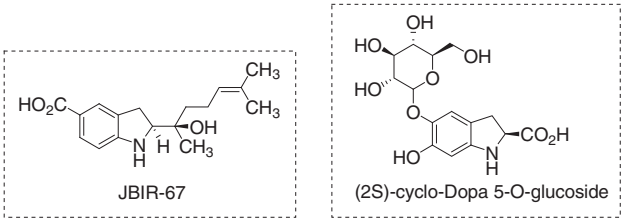
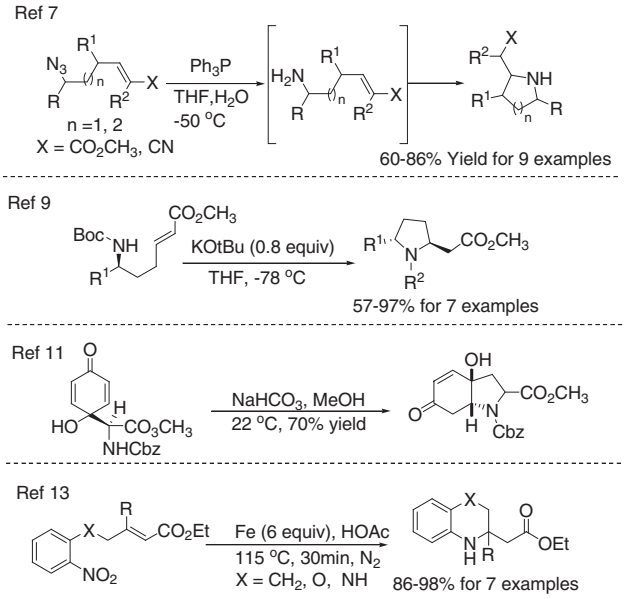


Figure 1. Indoline frameworks present in natural products.

Scheme 1. Examples of intramolecular *aza*-Michael reaction.

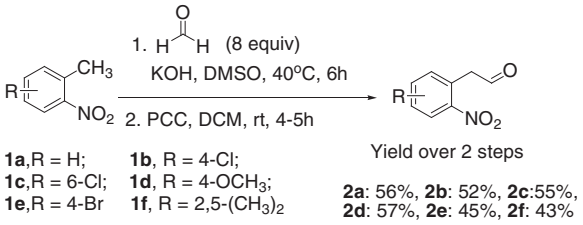


DMSO as solvent (Scheme 2). Upon purification, the alcohols were subjected to mild PCC oxidation to afford the corresponding aldehydes. All aldehydes are known compounds, and their spectral data are in complete accordance with the literature values. Synthesis of the α,β-unsaturated carbonyl compound in which the neighboring methylene carbon is also in a benzyilic position is often troublesome because of the possibility for double bond migration [15].

Samarium diiodide has been shown to be effective in the coupling of aldehydes to dibromoacetic acid [16], ethyldibromoacetate [17] and dichloroacetamide [18] in which the elimination reaction proceeds with very high *E* diastereoselectivity. SmI_2 is a well-known reducing agent of arylnitro groups to anilines [19]; thus, we envisaged a tandem reaction resulting in the corresponding indolines from aldehydes **2a–e** in a one-pot procedure. Our investigations exploring the substrate scope are summarized in Table 1.

We opted for a THF–MeOH solvent mixture given that the literature precedence indicated this to be the best in which reduction of the nitro group occurs readily under this condition. Generally, yields were good irrespectively of the electronic or steric nature of the aryl substituent, to give the

Scheme 2. Synthesis of aldehydes **2a–f** by a nucleophilic substitution – oxidation protocol.



1a,R = H; **1b**, R = 4-Cl;
1c,R = 6-Cl; **1d**, R = 4-OCH_3;
1e,R = 4-Br **1f**, R = 2,5-$(CH_3)_2$

2a: 56%, **2b**: 52%, **2c**:55%,
2d: 57%, **2e**: 45%, **2f**: 43%

expected indolines **3a–f** (entries 1–6). It appears that the addition of dibromoacetic acid is significantly faster than the nitro reduction and therefore allowing the obtainment of the indoline product in good yields. The slightly acidic nature of the reaction mixture is probably responsible for the solvolysis of the product that results in the formation of a pendant ester. Cyclization is easily confirmed by absence of the olefinic hydrogen signals and the appearance of a methine double doublet at ~3.30 ppm in the ^1H NMR spectra. The purity of the compounds was confirmed by elemental analysis and high resolution mass spectrometry.

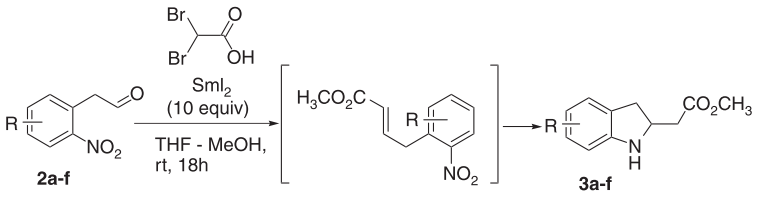
Our curiosity was drawn towards the application of this strategy for the synthesis of six and seven-membered rings. In contrast to the group of Bunce, we pursued the synthesis of the necessary substrate for the intramolecular cyclization reaction employing a palladium catalyzed coupling reaction, which upon double bond migration yields the desired aldehydes. This strategy was advantageous given that it permitted extension of the alkyl chain by employing the appropriate unsaturated alcohol (Scheme 3).

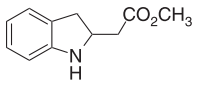
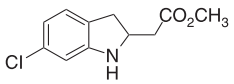
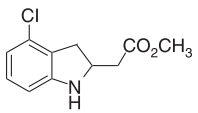
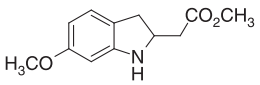
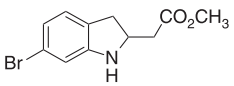
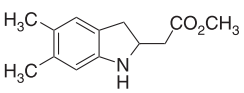
This now set the stage for the application of the present methodology for the preparation of the desired heterocycle compound. Heterocycle **5** was obtained in good yield as an oil after purification, and it was fully characterized by NMR spectroscopy with all ^1H and ^{13}C signals being assigned and in agreement with the literature data [20]. In contrast, substrate **4b** furnished only the aniline **6**, and intramolecular *aza*-Michael addition did not proceed to afford the expected tetrahydrobenzoazepine. Although the 7-exo-trig heterocyclization is favored under Baldwin's rules, the *aza*-Michael reaction is potentially reversible, and the subtle interplay of entropic and stereo-electronic factors seem to disfavor cyclization on this occasion.

In summary, we have developed a convenient methodology for the synthesis of a variety of indolines via a domino nitro reduction–intramolecular *aza*-Michael reaction. Using 10 equivalents of SmI_2, modest to good yields could be realized for the obtainment of both indoline and 1,2,3,4-tetrahydroquinoline heterocyles by this approach. A limitation was encountered when an attempt was made to extend this methodology to the synthesis of 2,3,4,5-tetrahydrobenzoazepines. Work is ongoing in

Table 1

Evaluation of substituted 2-(2-nitrophenyl)acetaldehyde derivatives.



Entry	Substrate	Product	Yield (%)
1	**2a**	 **3a**	67
2	**2b**	 **3b**	59
3	**2c**		61
4	**2d**	 **3d**	64
5	**2e**	 **3e**	57
6	**2f**	 **3f**	58

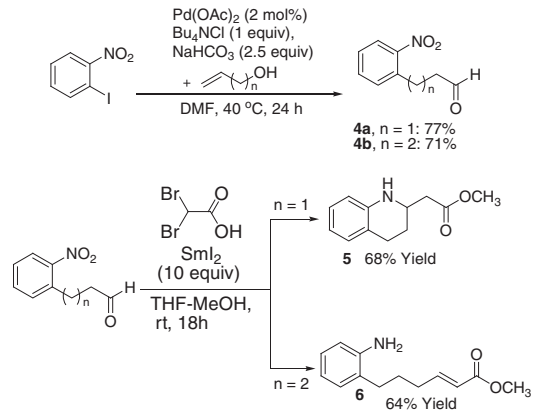
our group to develop new strategies toward the synthesis of medium sized benzo-fused nitrogen heterocycles.

EXPERIMENTAL

All commercial reagents were used as received. Anhydrous solvents were purchased from Sigma Aldrich (St. Louis, MO). Column chromatography was performed using silica gel 200–400 mesh. TLC analysis was performed using silica gel plates, using ultraviolet light (254 nm) or vanillin solution for visualization. Melting points are uncorrected. IR spectra were recorded using samples that were either prepared as a liquid film between NaCl plates or pressed into KBr discs. Elemental analyses (C, H, N, S) were conducted using the PerkinElmer 2400 Series; their results were found to be in good agreement (±0.3%) with the calculated values. For NMR data, the chemical shifts are reported in δ (ppm) referenced to residual protons and ^{13}C signals in deuterated chloroform. The coupling constants (*J*) are expressed in Hertz (Hz).

Synthesis of aldehydes 2a–f. To a stirred solution of substituted 2-nitrotoluene (90 mmol) in DMSO (200 mL) were added *para*-formaldehyde (720 mmol) and KOH (85% aqueous solution, 0.25 mol) dropwise over 10 min at 0°C, and then the reaction

Scheme 3. Synthesis of tetrahydroquinoline **5** and compound **6**.



mixture was stirred for an additional 18 h. The reaction mixture was poured into sat. NH_4Cl and extracted with chloroform (4× 100 mL). The extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (5–50% EtOAc in hexane) to give substituted 2-(2-nitrophenyl)ethanol **1a–e**. Spectroscopic data are in accordance with reported values: **1a** [21], **1b** [22], **1c** [23], **1d** [24], and **1e** [25].

To a solution of the substituted 2-nitrophenethyl alcohols **1a–e** (1 g, 6 mmol) in dry DCM (50 mL) was added PCC (1.9 g, 9 mmol). The resultant mixture was stirred at room temperature for 3 h and dried over $MgSO_4$. The filtrate was concentrated to dryness under reduced pressure, and the residual material was purified by column chromatography to give substituted 2-nitrophenylacetaldehyde **2a–e** (43–57% over two steps). Spectroscopic data are in accordance with reported values: **2a** [26], **2b** [27], **2c** [28], and **2d,f** [29].

Synthesis of aldehydes 4a and 4b. In a typical procedure for the synthesis of the aldehyde, a Schlenk tube equipped with a stir bar was charged with 2-nitroiodobenzene (8 mmol), allylalcohol or 3-buten-1-ol (18 mmol), sodium hydrogencarbonate (35.0 mmol), tetra-*n*-butylammonium chloride (8 mmol), and palladium acetate (2 mol%). Anhydrous DMF (15 mL) was added, and the black reaction mixture was heated to 40°C for 24 h. Upon completion, the solution was cooled to room temperature, diluted with EtOAc (25 mL), and filtered, and the solvent was removed under reduced pressure. The oily residue was purified by column chromatography to afford either **4a** (77%) or **4b** (71%) depending on the unsaturated alcohol employed.

3-(2-Nitrophenyl)propanal (4a). Pale yellow oil; $R_f = 0.1$ (hexanes/EtOAc, 4:1). Spectroscopic data are in accordance with the literature values [24]. υ_{max} (thin film, cm^{-1}): 3422, 3067, 2897, 2829, 2727, 1721, 1609, 1576, 1519, 1452, 1344, 1199, 1164, 1143, 1054, 1022, 850, 785, 742, 704, 662, 635; δ_H (400 MHz, $CDCl_3$): 9.85 (1H, s), 7.98 (1H, d, *J* 8.0), 7.58 (1H, t, *J* 8.0), 7.43–7.46 (2H, m), 3.25 (2H, t, *J* 7.6), 2.94 (2H, t, *J* 7.6); δ_C (100 MHz, $CDCl_3$): 200.4, 149.2, 135.8, 133.4, 128.5, 127.7, 125.0, 44.5, 25.8; MS *m/z* (EI): calcd for $C_9H_9NO_3$ 179.0582, found 179.0567. *Anal.* Calcd for $C_9H_9NO_3$: C, 60.33%; H, 5.06%; N, 7.82%. Found: C, 60.30%; H, 5.09%; N, 7.86%.

4-(2-Nitrophenyl)butanal (4b). Pale yellow oil; $R_f = 0.4$ (hexanes/EtOAc, 13:7); υ_{max} (thin film, cm^{-1}): 3427, 2940, 2873, 2878, 2827, 2727, 1715, 1609, 1527, 1480, 1409, 1347, 1244, 1166, 1144, 1054, 957, 859, 786, 743, 704, 665, 635; δ_H (400 MHz, $CDCl_3$): 9.83 (1H, s), 7.95 (1H, d, *J* 8.4), 7.59 (1H, t, *J* 8.4), 7.41–7.44 (2H, m), 2.97 (2H, t, *J* 7.2), 2.60 (2H, t, *J* 7.2), 2.01 (2H, quintet, *J* 7.2); δ_C (100 MHz, $CDCl_3$): 201.8, 149.3, 136.4, 133.1, 131.9, 127.4, 124.9, 43.3, 32.2, 23.1; MS *m/z* (EI): calcd for $C_{10}H_{11}NO_3$ 193.0739, found 193.0745. *Anal.* Calcd for $C_{10}H_{11}NO_3$: C, 62.17%; H, 5.74%; N, 7.25%. Found: C, 62.20%:;H, 5.79%; N, 7.26%.

General method for the synthesis of indoline derivatives. In a Schlenk tube (25 mL) equipped with a magnetic stir bar was charged dibromoacetate (2 mmol) and the corresponding aldehyde (2 mmol) in 5 mL of a 1:1 mixture of THF–MeOH. Next, 20 mmol of a 0.1*M* solution of SmI_2 was added slowly by syringe in THF, and the reaction mixture was stirred at room temperature for 18 h. Upon completion as determined by TLC, the reaction was quenched with aqueous 0.1*M* HCl (20 mL), and the organic layer was extracted with chloroform (3× 25 mL). The combined organic extracts were dried over MgSO4, and the solvent was removed under vacuum to afford an oily residue that was purified by flash chromatography on silica gel (hexane/EtOAc 8:1 to 4:1) providing the title compounds.

Methyl 2-(indolin-2-yl)acetate (3a). The product was obtained as a pale yellow oil; $R_f = 0.5$ (hexanes/EtOAc, 7:3); υ_{max} (thin film, cm^{-1}): 3356, 2940, 1622, 1456, 1315, 1262, 1157, 1043, 935, 869, 751; δ_H (400 MHz, $CDCl_3$): 7.12 (1H, d, *J* 7.6), 7.09 (1H, t, *J* 7.6), 6.79 (1H, t, *J* 7.6), 6.73 (1H, d, *J* 7.6), 5.67 (1H, br s, NH), 4.28–4.31 (1H, m), 3.66 (3H, s), 3.26 (1H, dd, *J* 8.4, 15.2), 2.77–2.68 (3H, m); δ_C (100 MHz, $CDCl_3$): 172.1, 148.3, 128.8, 127.7, 124.8, 120.3, 110.9, 56.0, 51.8, 40.2, 35.7; MS *m/z* (EI): calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0942. *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09%; H, 6.85%; N, 7.32%. Found: C, 69.15%; H, 6.87%; N, 7.29%.

Methyl 2-(6-chloroindolin-2-yl)acetate (3b). The product was obtained as a pale yellow oil; $R_f = 0.4$ (hexanes/EtOAc, 7:3); υ_{max} (thin film, cm^{-1}): 3354, 2942, 1624, 1456, 1316, 1268, 1152, 1043, 934; δ_H (400 MHz, $CDCl_3$): 7.01 (1H, d, *J* 7.6), 6.72 (1H, d, *J* 7.6), 6.56 (1H, s), 5.72 (1H, br s, NH), 4.23–4.30 (1H, m), 3.64 (3H, s), 3.27 (1H, dd, *J* 8.5, 15.0), 2.76–2.68 (3H, m); δ_C (100 MHz, $CDCl_3$): 172.4, 143.3, 133.5, 124.7, 122.8, 120.5, 110.3, 56.2, 51.8, 40.5, 35.9; MS *m/z* (EI): calcd for $C_{11}H_{12}ClNO_2$ 225.0557, found 225.0552. *Anal.* Calcd for $C_{11}H_{12}ClNO_2$: C, 58.54%; H, 5.36%; N, 6.21%. Found: C, 58.55%; H, 5.39%; N, 6.25%.

Methyl 2-(4-chloroindolin-2-yl)acetate (3c). The product was obtained as a pale yellow solid mp 57–59°C; $R_f = 0.37$ (hexanes/EtOAc, 7:3); υ_{max} (KBr disc, cm^{-1}): 3350, 2941, 1627, 1447, 1310, 1269, 1174, 1157, 1051, 1040, 934; δ_H (400 MHz, $CDCl_3$): 7.06–7.02 (2H, m), 6.58 (1H, s), 5.72 (1H, br s, NH), 4.23–4.30 (1H, m), 3.69 (3H, s), 3.29 (1H, dd, *J* 8.5, 15.0), 2.76–2.68 (3H, m); δ_C (100 MHz, $CDCl_3$): 170.9, 151.3, 135.2, 127.9, 122.6, 118.5, 112.0, 55.5, 51.1, 40.0, 34.5; MS *m/z* (EI): calcd for $C_{11}H_{12}ClNO_2$ 225.0557, found 225.0555. *Anal.* Calcd for $C_{11}H_{12}ClNO_2$: C, 58.54%; H, 5.36%; N, 6.21%. Found: C, 58.50%; H, 5.34%; N, 6.22%.

Methyl 2-(6-methoxyindolin-2-yl)acetate (3d). The product was obtained as a pale yellow oil; $R_f = 0.35$ (hexanes/EtOAc, 7:3); υ_{max} (thin film, cm^{-1}): 3345, 2949, 1620, 1466, 1310, 1275, 1172, 1163, 1100, 974; δ_H (400 MHz, $CDCl_3$): 7.11 (1H, d, *J* 7.6), 6.14 (1H, d, *J* 7.6), 6.02 (1H, s), 5.51 (1H, br s, NH), 4.23–4.30 (1H, m), 3.72 (3H, s), 3.65 (3H, s), 3.29 (1H, dd, *J* 8.5, 15.0), 2.76–2.68 (3H, m); δ_C (100 MHz, $CDCl_3$): 173.3, 153.7, 145.3,

124.1, 123.8, 124.5, 115.0, 56.2, 55.2, 51.8, 40.5, 36.0; MS *m/z* (EI): calcd for $C_{12}H_{15}NO_3$ 221.1052, found 221.1059. *Anal*. Calcd for $C_{12}H_{15}NO_3$: C, 65.14%; H, 6.83%; N, 6.33%. Found: C, 65.18%; H, 6.89%; N, 6.29%.

Methyl 2-(6-bromoindolin-2-yl)acetate (3e). The product was obtained as a pale yellow oil; $R_f = 0.4$ (hexanes/EtOAc, 7:3); υ_{max} (thin film, cm^{-1}): 1721, 1625, 1473, 1441, 1394, 1380, 1379, 1328, 1299, 1255, 1252, 1175, 1055, 1027, 904; δ_H (400 MHz, $CDCl_3$): 7.03 (1H, d, *J* 7.6), 6.70 (1H, d, *J* 7.6), 6.59 (1H, s), 5.70 (1H, br s, NH), 4.21–4.30 (1H, m), 3.65 (3H, s), 3.30 (1H, dd, *J* 8.5, 15.0), 2.73–2.68 (3H, m); δ_C (100 MHz, $CDCl_3$): 172.1, 143.5, 133.2, 124.7, 122.5, 121.5, 113.5, 56.2, 52.3, 41.2, 36.9; MS *m/z* (EI): calcd for $C_{11}H_{12}BrNO_2$ 269.0051, found 269.0058. *Anal*. Calcd for $C_{11}H_{12}BrNO_2$: C, 48.91%; H, 4.48%; N, 5.19%. Found: C, 48.95%; H, 4.49%; N, 5.21%.

Methyl 2-(5,6-dimethylindolin-2-yl)acetate (3f). The product was obtained as a pale yellow oil; $R_f = 0.37$ (hexanes/EtOAc, 7:3); υ_{max} (thin film, cm^{-1}): 3080, 2979, 2939, 2885, 2861, 1653, 1619, 1150, 1045; δ_H (400 MHz, $CDCl_3$): 7.24 (1H, s), 6.90 (1H, s), 4.96 (1H, br s, NH), 4.25–4.29 (1H, m), 3.67 (3H, s), 3.32 (1H, dd, *J* 8.5, 15.0), 2.77–2.65 (3H, m), 2,22 (3H, s), 2.17 (3H, s); δ_C (100 MHz, $CDCl_3$): 171.0, 137.3, 135.2, 131.9, 127.6, 126.5, 115.4, 55.5, 51.1, 40.0, 34.5, 20.2, 19.4; MS *m/z* (EI): calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1255. *Anal*. Calcd for $C_{13}H_{17}NO_2$: C, 71.21%: H, 7.81%: N, 6.39%. Found: C, 71.20%: H, 7.84%: N, 6.32%.

Methyl 2-(1,2,3,4-tetrahydroquinolin-2-yl)acetate (**5**). $R_f = 0.3$ (hexanes/EtOAc, 4:1); υ_{max} (thin film, cm^{-1}): 3396, 2981, 2934, 2846, 1726, 1607, 1586, 1485, 1445, 1351, 1275, 1188, 1114, 1028, 931, 853, 810, 749; δ_H (400 MHz, $CDCl_3$): 7.04–7.09 (2H, m), 6.69 (1H, t, *J* 6.4), 6.56 (1H, d, *J* 8.0), 4.54 (1H, br s, NH), 3.77–3.80 (1H, m), 3.69 (3H, s), 2.89–2.91 (1H, m), 2.69–2.83 (1H, m), 2.52 (2H, d, *J* 6.0), 1.99–2.02 (1H, m), 1.71–1.80 (1H, m); δ_C (100 MHz, $CDCl_3$): 172.3, 144.1, 129.3, 126.9, 120.9, 117.4, 114.6, 57.6, 47.8, 41.0, 28.1, 25.7; MS *m/z* (EI): calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1110. *Anal*. Calcd for $C_{12}H_{15}NO_2$: C, 70.22%; H, 7.37%; N, 6.82%. Found: C, 70.20%; H, 7.34%; N, 6.87%.

(***E***)-**Methyl 6-(2-aminophenyl)hex-2-enoate** (**6**). The product was obtained as a pale yellow oil (161 mg, 73%); $R_f = 0.5$ (hexanes/EtOAc, 7:3); υ_{max} (thin film, cm^{-1}): 3375, 2890, 2862, 1711, 1651, 1624, 1497, 1457, 1368, 1273, 1186, 1154, 1093, 1039, 978, 860, 750; δ_H (400 MHz, $CDCl_3$): 7.04–7.11 (3H, m), 6.78 (1H, t, *J* 7.6), 6.71 (1H, d, *J* 7.6), 5.90 (1H, dt, *J* 1.4, 15.6), 3.65 (3H, s), 3.62 (2H, br s, NH_2), 2.56 (2H, t, *J* 7.6), 2.33 (2H, q, *J* 7.6), 1.86 (2H, quintet, *J* 7.6); δ_C (100 MHz, $CDCl_3$): 166.6, 148.6, 144.1, 129.5, 127.2, 125.7, 121.8, 118.8, 115.7, 57.2, 31.9, 30.6, 26.9; MS *m/z* (EI): calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1253. *Anal*. Calcd for $C_{13}H_{17}NO_2$: C, 71.21%: H, 7.81%: N, 6.39%. Found: C, 71.25%: H, 7.89%: N, 6.37%.

Acknowledgments. Authors gratefully acknowledge the generous financial support from the Brazilian funding agencies Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

REFERENCES AND NOTES

[1] Naito, T. Chem Pharm Bull 2008, 56, 1367.
[2] Michael, J. P. J. Nat Prod Rep 1996, 13, 73.
[3] Liu, D.; Zhao, G.; Xiang, L. Eur. J. Org. Chem 2010, 3975.
[4] Kozlov, N. G.; Gusak, K. N.; Kadutskii, A. P. Chem. Heterocycl. Compd 2010, 46, 505.
[5] Motohashi1, K.; Nagai, A.; Takagi, M.; Shin-ya, K. J Antibiot 2011, 64, 281.
[6] Wyler, H.; Meuer, U.; Bauer, J.; Stravs-Mombelli, L. Helvetica Chimica Acta 1984, 67, 1348.
[7] Knouzi, N.; Vaultier, M.; Toupet, L.; Carrie, R. Tetrahedron Lett 1987, 28, 1757–1760.
[8] Fustero, S.; Moscardo, J.; Sanchez-Rosello, M.; Rodriguez, E.; Barrio, P. Org Lett 2010, 12, 5494.
[9] Gärtner, M.; Weihofen, R.; Helmchen, G. Chem Eur J 2011, 17, 7605.
[10] Enkisch, C.; Schneider, C. Eur. J. Org. Chem 2009, 5549.
[11] Wipf, P.; Kim, Y. Tetrahedron Lett 1992, 33, 5477.
[12] Bland, D.; Chambournier, G.; Dragan, V.; Hart, D. J. Tetrahedron 1999, 55, 8953.
[13] Bunce, R. A.; Herron, D. M.; Ackerman, M. L. J Org Chem 2000, 65, 2847.
[14] Labadie, S. S.; Parmer, C. Synth. Commun 2011, 41, 1752.
[15] Moreira, N. D. F.; de Oliveira, T. T.; Nagem, T. J.; Taylor, J. G. Heterocycl. Commun 2011, 17 (5–6), 203.
[16] Concellón, J. M.; Concellón, C. J Org Chem 2006, 71, 1728.
[17] Concellon, J. M.; Concellon, C.; Mejica, C. J Org Chem 2005, 70, 6111.
[18] Concellon, J. M.; Rodriguez-Solla, H.; Concellon, C.; Simal, C.; Alvaredo, N. J Org Chem 2010, 75, 3451.
[19] Yu, C.; Liu, B.; Hu, L. J Org Chem 2001, 66, 919.
[20] Gilchrist, T. L.; Rahmam, A. J Chem Soc Perkin Trans 1 1998, 1203.
[21] Wierenga, W.; Harrison, A. W.; Evans, B. R.; Chidester, C. G. J Org Chem 1984, 49, 438.
[22] Fielden, R.; Meth-Cohn, O.; Price, D.; Suschitzky, H. J Chem Soc Perkin Trans 1 1973, 696.
[23] Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. J Org Chem 2006, 71, 4255.
[24] Laboratórios Serono as, Patent: WO2008/101979 A1, 2008.
[25] Meiji Seika Kaisha Ltd. Patent: EP2151447 A1, 2010.
[26] Yamane, Y.; Liu, X.; Hamasaki, A.; Ishida, T.; Haruta, M.; Yokoyama, T.; Tokunaga, M. Org Lett 2009, 11, 5162.
[27] Raucher, S.; Koolpe, G. A. J Org Chem 1983, 48, 2066.
[28] McIntosh, M. L.; Johnston, R. C.; Pattwong, O.; Ashburn, B. O.; Naffziger, M. R.; Cheong P. H.; Carter, R. G. J Org Chem 2012, 77, 1101.
[29] Chernyak, N.; Buchwald, S. L. J Am Chem Soc 2012, 134, 12466.